

## REMARKS

Claims 2, 6, 16, 17, 19-21, 28 and 30 are pending in this application and are presented for reconsideration. No claims have been currently cancelled, amended or added. The claims are identical to those of applicants' previous amendment.

In said amendment applicants amended their claims in order to more particularly point out and distinctly claim a preferred aspect of their invention. Thus, all of the present claims are directed to applicants' inventive method of preparing a pharmaceutical formulation of a lipophilic pharmaceutical active agent in the form of an aqueous monodisperse nanodispersion having a Gaussian distribution.

Claims 2, 6, 10, 16-17, 19-21, 28 and 30 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Yiv et al., U.S. Patent 6,245,349 in view of Weder WO 96/37192 and newly cited EP-A 0 349 160.


The first 2 references have been cited in earlier Office Actions and exhaustively discussed. Specifically, they disclose the preparation of an o/w nanodispersion by pre-mixing a phospholipid, a polyethoxylated sorbitan ester (TWEEN 80) as emulsifier, an oil, and either propylene glycol or ethanol, and adding the mixture to an aqueous phase.

Newly cited EP-A-349150 teaches the preparation of a transparent emulsion from a lipid phase containing lecithin, a surfactant (e.g. a polyethoxylated emulsifier), oil and an "aqueous solvent", by mixing it with a water phase. This is done using high pressure mixing equipment, e.g. "an emulsifier, such as a homomixer" or a device providing "a stronger shearing force than a homomixer (see page 4, lines 30 and 37-38, and the examples). The reference further teaches use of high amounts of certain alcohols as the "aqueous solvent", generically including ethanol, but with all the specific examples using glycols such as propylene glycol.

The examiner still regards the present component "polyethoxylated carbohydrate" as encompassing a polyoxyethylene sorbitan monooleate such as TWEEN 80. The examiner even attaches a reference showing the structure, which is in accordance with applicants' definition of this component in their previous amendment of January 25, 2005. However, the examiner draws from the correct descriptions of sorbitol as a sugar alcohol, and sorbitan as the anhydride form of sorbitol, the **clearly erroneous** conclusion that sorbitan is a carbohydrate (page 8, lines 8-9).

As already explained in applicants' previous amendment, sorbitol,  $C_6H_{14}O_6$ , is obtained by hydrogenation of the carbohydrate glucose  $C_6H_{12}O_6$  (for molecular formulas see upper reaction scheme on page 1059 of the Wade textbook, ORGANIC CHEMISTRY, previously submitted). Sorbitol is a reaction product of glucose, not a derivative, and the ratio of hydrogen to oxygen in sorbitol is not the same as exists in water.

$$\text{C}_6\text{H}_{14}\text{O}_6 - \text{H}_2\text{O} = \text{C}_6\text{H}_{12}\text{O}_5$$


  
 (sorbitol)  (sorbitan)

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In the corresponding polyethoxylated sorbitan product, 3 of the 4 free OH groups of sorbitan are etherified with polyethoxy; one is esterified with the fatty acid.

Both sorbitan and sorbitol clearly **differ** from a carbohydrate by **containing 2 more hydrogen atoms** than is possible for the corresponding carbohydrate. Any dehydrated carbohydrate, discussed by the examiner further below on the same page, can thus never be of the same constitution as a dehydrated sugar alcohol or anhydride thereof such as sorbitan.

All of this is clearly within the general knowledge of one skilled in the art and requires no further explanation or basis in the specification. Sorbitan is not a carbohydrate, and the term "carbohydrate" does not refer to a sugar alcohol or an anhydride thereof. Since sorbitan is not a carbohydrate, polyethoxylation of it cannot produce polyethoxylated carbohydrates.

As previously noted, the complete list of emulsifiers to be used according to the present invention is defined under component (b) of present claim 28, and this definition precisely distinguishes between compound classes to be used **as such** (e.g. polyethoxylated fatty alcohols or polyethoxylated carbohydrates), and compound classes requiring or allowing a chemical modification to be used as the emulsifier (i.e. polyethoxylated vitamin E **derivatives**, polyethoxylated lanolin and the **derivatives** thereof).

Consequently, the prior art sorbitan derivative mentioned by the examiner clearly is not embraced by the present claims.

It was the finding of the present invention that the use of the presently claimed polyethoxylated coemulsifiers together with ethanol brings about distinct advantages over other coemulsifiers, including those of the TWEEN type used by Yiv (US '349) or Weder (WO' 192) (see Dr. Supersaxo's Declaration of May 18, 2004), or the use of propylene glycol as recommended by Yiv and in EP'150 (see Dr. Supersaxo's Declaration of January 14, 2005).

These improvements appear to have been completely ignored by the examiner, who states that

- it would have been obvious to use ethanol in a composition as disclosed by Yiv, and
- it would have been obvious to use any polyethoxylated surfactant system as of EP'150 in combination with or in place of TWEEN 80,

and thus arrive at the present invention, as both measures would provide a reasonable expectation of success.

Applicants note that EP' 150 uses none of the polyethoxylated surfactant systems of the present claims.

Moreover, the prior art cited would, at best, lead the skilled person to expect that replacing propylene glycol by ethanol, and replacing TWEEN 80 by another surfactant as recommended by Yiv (high HLB > 12, see col. 6, lines 6-37) or as listed in EP'150 (e.g. a sugar fatty acid ester, see page 3, lines 25-34) would lead to equivalent results.

As shown in the 2 Declarations mentioned above, however, results are clearly improved rather than merely equivalent. Replacing propylene glycol by ethanol leads to a finer particle size, just as does replacing TWEEN 80 with one of the selected coemulsifiers of the presently claimed component (b).

Moreover, replacing TWEEN 80 in accordance with the recommendations given by Yiv or in EP'150 e.g. with a sugar fatty acid ester (saccharose monopalmitate, HLB = 15) led to particle sizes far beyond the nano scale and to preparations which were not transparent.

Thus, it is clear that the teachings of the references cited as a whole cannot provide a reasonable expectation of success to the skilled person trying to prepare a nanodispersion.

Further, while particle sizes obtained in prior art may, at least in some instances, be within the limits of the present claims (i.e. < 50nm), it deserves emphasis that the present nanoparticles are obtained by a different means (i.e. using a different coemulsifier and/or different alcohol) and in a better quality (i.e. smaller dimension) than those of prior art. Smaller particle sizes are relevant because particle sizes determine both stability and administration characteristics of the formulation. It appears not in accordance with the general examination procedure to object to a claim that does not contain a limitation with respect to the effect of the invention, while it does contain a limitation with respect to the means for achieving this effect.

Applicants submit herewith a further Declaration from Dr. Andreas Supersaxo, signed on October 4, 2005, which presents comparisons between nanodispersions containing two different coemulsifiers within the scope of the present claims versus a formulation containing TWEEN 80 according to the

prior art. Said Declaration shows that the long term stability of formulations containing the two coemulsifiers within the scope of the present claims is clearly better than that of the formulation containing TWEEN 80. After 12 months of storage at 40°C, the present formulations containing SOLUTOL HS 15 or CREMOPHOR EL are visibly unchanged, while the formulation containing TWEEN 80 has become milky.

Applicants aver that it could not have been expected from the teachings of the cited references that the present formulations would bring about a distinctly improved storage stability and thus provide a distinct advantage for pharmaceutical applications.

The distinct advantages of the present invention, as shown now in multiple declarations, clearly were not to be expected at the time present invention was made. Thus, applicants aver that the subject matter presently claimed fully meets the requirements for a patent grant.

Reconsideration and withdrawal of the rejection of claims 2, 6, 10, 16-17, 19-21, 28 and 30 is respectfully solicited in light of the remarks *supra*.

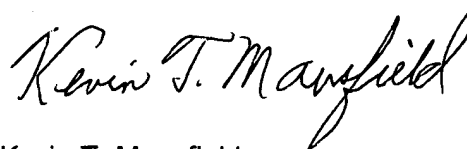
Claims 2, 6, 10, 16-17, 19-21, 28 and 30 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over recently allowed claims 32-37 of copending application number 10/016,903. The examiner points out in the middle of page 6 that a non-statutory double patenting rejection is a judicially created doctrine grounded in public policy. Its purpose is to prevent the unjustified or improper time-wise extension of the "right to exclude" granted by a patent by prohibiting the issuance of claims in a second patent that are not patentably distinct from the claims of a first patent. It may be overcome by filing a terminal disclaimer.

Responsive thereto a terminal disclaimer over copending application number 10/016,903 accompanies this amendment.

Since there are no other grounds of objection or rejection, passage of this application to issue with claims 2, 6, 10, 16-17, 19-21, 28 and 30 is earnestly solicited.

Applicants submit that the present application is in condition for allowance. In the event that minor amendments will further prosecution, Applicants request that the examiner contact the undersigned representative.

Respectfully submitted,



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Enclosures: 2 references, Petition for Extension of Time, Terminal Disclaimer,  
Declaration

**OCT 19 2005**

# GLOSSARY OF CHEMICAL TERMS

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work done by the system. Calorimetric measurements are useful in determining important thermodynamic properties of substances, for example, heat capacity, entropy, and free energy.

**calorizing.** See cementation.

**camphene.** See camphor.

**camphor.** An unusual vegetable product, camphor is derived by distilling the wood of a species of tree found chiefly in Taiwan. Chemically it is a ketone, with the formula  $C_{10}H_{16}O$  and is characterized by a strong, penetrating odor. It is made synthetically from pinene by heating with sodium acetate to form camphene ( $C_{10}H_{16}$ ), from which camphor is then derived by reaction with nitrobenzene and acetic acid. Camphor is flammable and evolves explosive vapors on heating. It is used industrially as a plasticizer for nitrocellulose and was a basic ingredient of the first synthetic plastic (Hyatt, 1869). It is also used as an insecticide and moth-proofing agent and in medicine (camphor oil).

**Canada balsam.** See balsam; Nicol.

**Cannizzaro, Stanislao** (1826-1910). Born in Italy, Cannizzaro extended the research of Avogadro on the molecular concentrations of gases and thus was able to prove the distinction between atoms and molecules. His investigations of atomic weights helped to make possible the discovery of the Periodic Law by Mendeleev. His research in organic chemistry led to the establishment of the Cannizzaro reaction involving the oxidation-reduction of an aldehyde in the presence of concentrated alkali.

**caprolactam.** The monomer used in the manufacture of nylon 6, originally developed in Germany; it is derived by several methods from cyclohexane or from phenol, catalytic synthesis being involved, together with complex molecular rearrangements. In addition to its use in synthetic fibers, it is an ingredient of paints and plasticizers and also serves as a cross-linking agent. Its structural formula is  $\text{CH}_2(\text{CH}_2)_4\text{NHCO}$ . It is furnished in both solid and liquid forms and is water-soluble. It can be used to synthesize the amino acid lysine. See also nylon.

**capryl alcohol.** See octyl alcohol.

**capture.** See absorption (3).

**carbamide.** See urea; amide.

**carbaryl.** See insecticide.

**carbazole.** See anthracene.

**carbene.** A short-lived and strongly reactive

group containing a carbon atom having only six instead of eight valence electrons. The composition of this group, which is derived by the action of ultraviolet radiation on ketone, is  $:\text{CH}_2$ . Because of its lack of electrons, the carbon atom has only two valences, which accounts for the exceptional activity of carbene and its value as an initiator of organic reactions. Its behavior is similar to that of carbonium ions, carbanions, and free radicals, all of which contain unstable carbon. The term methylene is used synonymously. See also carbonium ion; free radical.

**carbide.** A compound composed of two constituents, namely, carbon and a metal or non-metal; examples are calcium carbide ( $\text{CaC}_2$ ), from which acetylene is made, aluminum carbide ( $\text{Al}_4\text{C}_3$ ), silicon carbide ( $\text{SiC}$ ), boron carbide ( $\text{B}_4\text{C}$ ), and tungsten carbide ( $\text{WC}$ ). Carbides are usually made by heating the reacting substances in an electric furnace. Some are characterized by extreme hardness and resistance to high temperature; these are used as abrasives and refractory furnace linings (silicon carbide) and for metal-cutting drills and similar tools (tungsten carbide). Carbides may be pulverized, mixed with a similarly powdered metal such as cobalt or iron, and compressed at high temperature to form so-called cemented carbides.

**carbocyclic.** Any cyclic compound in which only carbon atoms appear in the ring, e.g., cyclohexane (alicyclic) and benzene (aromatic). See also heterocyclic.

**carbohydrate.** A class of compounds which are basic components of plants of all types; they collectively constitute the most abundant group of natural organic substances. They include both simple compounds (sugars) and polymers of these (starches and cellulose), the latter being called polysaccharides. Carbohydrate molecules are composed of carbon, hydrogen, and oxygen, the ratio of the last two being the same as exists in water. The atoms are so arranged that each molecule contains a hydroxyl group and a carbonyl group—a structure known as a saccharose unit. The simple sugars include fructose (levulose), glucose (dextrose), and sucrose; the polymers comprise all varieties of starches, seaweeds, natural gums, and cellulose. See also sugar; starch; cellulose; polysaccharide; seaweed; gum.

**carbolic acid.** See phenol.

**carbon.** An element.



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To obtain the nitrosyl chloride for producing the oxime, the following reactions are required: (1)  $\text{NH}_3$  is burned in air to produce  $\text{NO}_2$ :  $2\text{NH}_3 + 3\text{O}_2 \rightarrow \text{N}_2\text{O}_3 + 3\text{H}_2\text{O}$ ; (2) nitrosylsulfuric acid is made by reacting nitrogen trioxide with  $\text{H}_2\text{SO}_4$ :  $2\text{H}_2\text{SO}_4 + \text{N}_2\text{O}_3 \rightarrow 2\text{HNOSO}_4 + \text{H}_2\text{O}$ ; (3) nitrosyl chloride then is made by adding HCl to the nitrosylsulfuric acid:  $\text{HNOSO}_4 + \text{HCl} \rightarrow \text{NOCl} + \text{H}_2\text{SO}_4$ . High-pressure mercury lamps are used to effect the photochemical reaction. Any radiation of a wavelength shorter than 3,650 Å must be filtered out to avoid formation of tarry products. Critical factors that determine the yield of the process include temperature, the distance between the lamps and reactor, and the volume of the reactor. The crude caprolactam solution is neutralized with  $\text{NH}_3$ . The resulting mixture separates into an upper layer of crude caprolactam; the lower layer contains aqueous  $(\text{NH}_4)_2\text{SO}_4$ . An advantage claimed for this process is that only about one-half as much by-product  $(\text{NH}_4)_2\text{SO}_4$  is formed as compared to other processes.

**CAPTURE-RECAPTURE METHOD.** A method of estimating the size of populations of wild animals. A number are captured, marked and released unharmed. Later, a further sample is captured and the number of marked animals in it provides the basis of the estimate.

**CAPTURE RELEASE SAMPLING.** Sampling (Statistics).

**CAPUCHIN MONKEY.** Monkeys and Baboons.

**CAPYBARA.** Rodentia.

**CARACARA** (*Aves, Falconiformes*). South American birds of several species related to the hawks. They eat carrion but also catch living prey and sometimes rob other birds of their prey. One species, Audubon's caracara, *Polyborus cheriway*, occurs in the extreme southern parts of the United States. The chimachima is found from Panama to southern Brazil. The chimango is found in Tierra del Fuego and the southern part of the continent. See also *Falconiformes*.

**CARANGIDS** (*Osteichthyes*). Of the order *Percomorphi*, suborder *Percoidea*, the family *Carangidae*, the carangids are very fast and many of the species are excellent food fishes. They are well distributed worldwide in tropical and temperate waters. There are about 200 species, most of which are shaped something like the yellow jack (*Gnathanodon speciosus*). The latter fish occurs in the Indo-Pacific and attains a length of about 3 feet (0.9 meter). It possesses several vertical greenish stripes on a pale yellow body. The tail fin is sharply forked. The jack mackerel (*Trachurus symmetricus*) frequents the waters of the American Pacific coast. These fish are characterized by a sharp ridge adjacent the caudal peduncle of the tail. This is formed by a series of bony plates, sometimes called scutes.

Another interesting carangid is the Atlantic pompano (*Trachinotus carolinus*), a valuable food fish. Possessed of spectacular blue coloration on the back, the dirigible-shaped *Elagatis bipinnulatus* (Indo-Pacific rainbow runner) attains a length of about 4 feet (1.2 meters). The yellowtail (*Seriola dorsalis*) is a highly regarded sporting fish in the waters of Mexico and southern California and attains a length in excess of 3 feet (0.9 meter). The *Naucrates ductor* is the legendary pilot fish, reputed to lead ships and swimmers to safety. The legend has no foundation. The species of jack fishes frequenting the waters of the Palmyra Islands are reputed to be poisonous. However, a related species (*Caranx melampygus*), known as the black ulua, is widely sold in the Hawaiian Islands. The jacks and cavallas found in the Philippines are considered of premium commercial value, particularly when taken from the freshwater lakes on their return to the sea. Jacks are also found in New Guinea.

**CARAPACE.** A shield-like covering of the upper part of the body. In the crustaceans it is the body wall of the thorax and in the turtles and tortoises it is a complex structure made up of bony plates, including flattened ribs and vertebrae, covered with thin horny plates. The armor of the armadillo, composed of many bony plates developed from the skin and covered with horny plates, is also called a carapace.

**CARAPATO** (*Arachnida, Acarina*). Ticks of two species, found in tropical Africa and Central America, respectively. The African species is also called the tampan.

The wounds produced by these creatures are severe in themselves but their transmission of the germs of relapsing fever is a much greater danger.

**CARAWAY.** Umbelliferae.

**CARBAMATES.** Derivatives of the hypothetical carbamic acid,  $\text{H}_2\text{NCOOH}$ , which does not exist. The ethyl derivative urethane, prepared by heating urea in alcohol under pressure, by the reaction  $\text{H}_2\text{NC(=O)NH}_2 + \text{C}_2\text{H}_5\text{OH} \rightarrow \text{H}_2\text{NCOOC}_2\text{H}_5 + \text{NH}_3$ . Other derivatives are shown in the accompanying table.

**CARBAMIC ACID.** Herbicide; Insecticide.

**CARBANION.** An ion of the general formula  $\text{B}-\overset{\text{A}}{\underset{\text{D}}{\text{C}}}^-$ , where A, B

and D are substituent groups. Their importance in elucidating the mechanism of organic reactions is because a considerable proportion of all organic reactions involve carbanions, as others do carbonium ions and carbon free radicals (including carbene radicals). Many carbanion reactions involve removal of a proton from a carboxylic acid to form a carbanion. Many electrophilic substitution reactions involve carbanions. Carbanions are strong bases or nucleophiles. Many electrophilic substitution reactions that have carbanion intermediates are base-catalyzed since the basic reagent produces the basic carbanion. Because of the negative charge on carbanions, their structures are affected by cations, by attached substituents and particularly by the solvent.

**CARBENE.** The name quite generally used for the methylene radical,  $:\text{CH}_2$ . It is formed during a number of reactions. Thus the flash photochemical decomposition of ketene ( $\text{CH}_2=\text{C}=\text{O}$ ) has been shown to proceed in two stages. The first yields carbon monoxide and  $:\text{CH}_2$ , the latter then reacting with more ketene to form ethylene and carbon monoxide. Carbene reacts by insertion into a C—H bond to form a C—CH<sub>3</sub> bond. Thus carbene generated from ketene reacts with propane to form *n*-butane and isobutane. Carbene generated by pyrolysis of diazomethane reacts with diethyl ether to form ethylpropyl ether and ethylisopropyl ether.

Substituted carbenes are also known; chloroform reacts with potassium *t*-butoxide to form dichlorocarbene  $:\text{CCl}_2$ , which adds to double or triple carbon-carbon bonds to form cyclopropane derivatives.

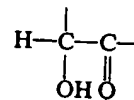
**CARBENICILLIN.** Antibiotic.

**CARBIDES.** Carbon; Iron Metals, Alloys, and Steels.

**CARBOCYCLIC COMPOUNDS.** Organic Chemistry.

**CARBOHYDRATE** (Nucleic Acids). Nucleic Acids and Nucleoproteins.

**CARBOHYDRATES.** These are compounds of carbon, hydrogen, and oxygen that contain the saccharose grouping (below), or its first reaction product, and in which the ratio of hydrogen to oxygen is the same as in water.



Carbohydrates are the most abundant class of organic compounds, representing about three-fourths of the dry weight of all vegetation. Carbohydrates are also widely distributed in animals and lower life forms. These compounds comprise one of the three major components (others are protein and fat) of the human diet, and indeed that of